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Impact of Introduction of the *Haemophilus influenzae* Type b Conjugate Vaccine into Childhood Immunization on Meningitis in Bangladeshi Infants

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Abstract

Objectives—Some Asian countries have been reluctant to adopt *Haemophilus influenzae* type b (Hib) conjugate vaccination because of uncertainty over disease burden. We assessed the impact of introduction of Hib conjugate vaccine into the Expanded Program on Immunization in Bangladesh on purulent and laboratory-confirmed *H influenzae* meningitis.

Study design—Within a well-defined catchment area around 2 surveillance hospitals in Dhaka, Bangladesh, we compared the incidence of Hib meningitis confirmed by culture, latex agglutination, and polymerase chain reaction assay among infants 1 year before and 1 year after introduction of Hib conjugate vaccine. We adjusted the incidence rate for the proportion of children who sought care at the surveillance hospitals.

Results—Among infants, the incidence of confirmed Hib meningitis decreased from 92-16 cases per 100 000 within 1 year of vaccine introduction (vaccine preventable incidence = 76; 95% CI 18, 135 per 100 000). The incidence of purulent meningitis decreased from 1659-1159 per 100 000 (vaccine preventable incidence = 500; 95% CI: 203, 799 per 100 000). During the same time period, there was no significant difference in the incidence of meningitis due to *Streptococcus pneumoniae*.

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Author Disclosures

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Conclusions—Introduction of conjugate Hib conjugate vaccine into Bangladesh Expanded Program on Immunization markedly reduced the burden of Hib and purulent meningitis.

Globally, 8 million episodes of serious disease are caused by *Haemophilus influenzae* type b (Hib) among children each year leading to an estimated one-half a million of deaths.[1] In Bangladesh, Hib has been identified as 1 of the 3 leading etiologic agents of childhood meningitis.

One-quarter of the cases of confirmed Hib meningitis die, and approximately one-quarter of survivors experience long-term disability.[2] Invasive Hib disease has been virtually eliminated from high-income countries where Hib conjugate vaccine has been introduced as part of the routine childhood immunization.[3-7] The high cost of the vaccine and controversy about the burden of disease in Asia has delayed widespread adoption of the vaccine in this region. However, recent data suggest that the incidence of Hib in Asia does not differ much from that of Europe in the prevaccine era of 25 per 100 000 for meningitis and at least 40 per 100 000 per year for invasive Hib disease at the age of 0-5 years.[8,9] The total burden of Hib probably is significantly greater as nonbacteremic Hib pneumonia remains mostly undetected.

Most of the evidence related to Hib disease burden is hospital-based prevalence estimates derived from a single or few hospitals or health care facilities.[10] These rates grossly underestimate disease incidence because they do not account for the population not served by these facilities, differing disease referral patterns, low lumber puncture rates, as well as suboptimal laboratory procedures.[9]

The World Health Organization now recommends Hib conjugate vaccine be incorporated in all routine infant immunization programs even in absence of local disease burden data.[11] The vaccine is being introduced in a number of Asian countries but few have evidence of effectiveness. In June 2009, the Government of Bangladesh introduced Hib conjugate vaccine into the national Expanded Program on Immunization (EPI), with support from GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunization), with the understanding that an increasing proportion of the vaccine cost would be borne by the Bangladeshi Government in subsequent years. The objective of this study was to assess the impact and coverage of this introduction of the Hib conjugate vaccine through the National EPI program on Hib meningitis and thereby permit the Government of Bangladesh to make informed decisions regarding future funding.

Methods

The study consisted of 2 components: hospital-based surveillance of meningitis and a community-based hospital catchment area assessment conducted twice (once in the prevaccine period and a second assessment postvaccination). We compared the incidence of Hib meningitis in hospitalized infants 1 year before and 1 year after the vaccine was introduced into the childhood immunization schedule.

Individual informed consent was obtained from the primary caretaker of the children before enrolling in the study. The study was approved by ethics committee at International Center

for Diarrheal Disease Research, B (icddr,b) and Johns Hopkins University, and exempted by Centers for Disease Control and Prevention ethics as it was deemed part of routine surveillance.

Hospital-Based Surveillance

On May 1, 2008, we initiated surveillance for Hib meningitis in 2 large pediatric hospitals in Dhaka, Bangladesh. Dhaka Shishu Hospital and Shishu Shasthya Foundation Hospital are 2 of the largest pediatric hospitals in Bangladesh. They provide primary, secondary, and tertiary care for severe childhood illnesses. Routine investigations with lumbar puncture are part of the standard of care at both of the hospitals for children who present with symptoms of meningitis. The aim of the hospital-based surveillance was to identify children with meningitis and to collect clinical specimens for laboratory diagnosis. Surveillance physicians regularly reviewed hospital admissions and identified patients <5 years of age who met a meningitis clinical case definition (children with new onset of fever with either altered mental status, new onset of seizures, or signs of a bulging fontanelle or stiff neck).

The surveillance physicians were trained in using maps to identify and enroll patients from within the limits of the catchment area of the hospital (outlined below). From these patients, the physicians collected data on demographics and clinical course of the disease using a standardized questionnaire and coordinated the collection of a sample of cerebrospinal fluid (CSF) on admission for laboratory diagnosis of meningitis. They collected a sample of urine in cases where CSF collection failed or was not advised. The specimens from both hospitals were tested at the Dhaka Shishu Hospital microbiology laboratory. Laboratory procedures for detection of *H influenzae* included culture of blood, CSF, latex agglutination test (LAT), and polymerase chain reaction (PCR). The isolates were serotyped by the slide agglutination method using type specific antisera (Murex, Kent, United Kingdom).[2] Hib was identified from culture negative CSF by LAT and/or PCR. Serotype of the culture negative cases was determined as b or non-b, by LAT and/or PCR.[2,12] Laboratory procedures for the detection of *Streptococcus pneumoniae* included culture of blood or CSF.

Defining Catchment Area

We conducted surveillance within the boundaries of the primary catchment area around the 2 surveillance hospitals. We defined the boundaries of the primary catchment area by identifying household locations of 100 children who had been discharged from the surveillance hospitals with a diagnosis of meningitis or encephalitis living within 1 hour of transport time from the hospitals. We consecutively enrolled children from the hospital who met our enrollment criteria and continued enrollment until we obtained 100 samples. Field researchers noted the geographical positional system co-ordinates of the house, which were plotted onto a map. We outlined a geographical area, which captured a majority (>80%) of these house locations, and labeled it as the primary catchment area of the 2 hospitals.

We superimposed a virtual grid over the catchment area, which divided it into 1748 equal sized 5 second (0.833°) latitude by 5 second longitude rectangles that corresponded in the community to an area of 142 by 153 meters. We used a random number generator to select 100 such rectangles for community assessment. In June 2008, the field team traveled to each

of the selected rectangles assisted by satellite photographs and remote sensing, and conducted a survey before introduction of Hib conjugate vaccine in each of the households whose front door was within the boundaries of the 100 randomly selected rectangles whose residents included a child <5 years of age. Among parents who consented, the interviewers collected the number and date of birth of children <5 years of age who lived in the household. Interviewers copied the vaccinations recorded on the child's vaccine card when a card was available, and asked the child's mother to recall vaccinations if the card was unavailable. In addition, the interviewers asked if any of the children <5 years of age in the household had developed a serious illness with acute onset of fever with either convulsions or unconsciousness or altered mental status in the preceding year (clinical meningoencephalitis) and the proportion who used either of the 2 surveillance pediatric hospitals during this illness. We defined a suspect case of meningoencephalitis as a child who had a serious illness with acute onset of fever with either convulsions or unconsciousness or altered mental status. We repeated this cross-sectional evaluation in August 2010 in a new random sample of 30 rectangles to reassess vaccine coverage after introduction of the Hib conjugate vaccine into the national EPI program. We used a smaller sample for the 2010 survey because it provided sufficient precision to estimate immunization coverage; we did not aspire to reassess hospital utilization.

Hib Vaccination Program

Hib conjugate vaccine in pentavalent formulation, Quinvaxem (diphtheria-tetanus-pertussis (DTP)-hepatitis B-Hib fully liquid combined vaccine) manufactured by Novartis (Basel, Switzerland) was introduced into the Bangladesh EPI program on June 10, 2009. The vaccine was targeted at children aged 6, 10, and 14 weeks. The first children eligible to receive a 6-week dose of the pentavalent vaccine on June 10, 2009 were born on April 15, 2009, and received their third dose by August 2009.

Pre- and Postvaccine Periods

We designated cases among children born between May 1, 2008 (commencement of our hospital based surveillance) to April 15, 2009, as belonging to our prevaccine period, and children born on or after April 19, 2009- May 15, 2011, as belonging to our postvaccine period, based on eligibility to have received Hib conjugate vaccine. We restricted our analysis among children <12 months of age as there was only 1 year of postintroduction data available at the time of reporting, and this is the age group most at risk for Hib meningitis.

Data Analyses

This surveillance is designed to measure Hib disease in children < age 5 years, but in this post-Hib conjugate vaccine introduction assessment, we limited the analysis to children ≤1 year of age because so few children had reached an older age, and we wanted to compare children of similar age before and after vaccine introduction. We calculated person-time denominators as the years of follow-up from birth until the outcome of interest: meningitis or death, or 1-year of age or the end of study follow-up. We aggregated observed person-time for children in surveyed rectangles and then projected for the total number of infants in the entire catchment area. We defined a case of confirmed Hib meningitis as confirmation by culture, LAT or PCR of Hib in the CSF or LAT for Hib antigen in urine at the dilution

≥1:16 in a child presenting with clinical meningitis. We also considered a case of clinical meningitis with Hib isolated from blood culture as confirmed Hib meningitis. We classified a case as purulent meningitis if a child who presented with clinical meningitis had CSF with a cell count of >100 polymorphonuclear leukocytes cells/mm^3. We calculated crude incidence by dividing the number of confirmed Hib meningitis cases by the total person-time contributed by infants during the pre- and the postvaccine periods. We then adjusted these crude rates by the proportion of suspect meningoencephalitis cases in the catchment area who sought care at the 2 surveillance hospitals. To analyze the impact of vaccine introduction and calculate the vaccine preventable incidence rate, we took the difference in incidence of Hib and purulent meningitis before and after introduction of the vaccine. We evaluated the incidence of culture confirmed pneumococcal meningitis as a comparison that would be affected by any change in surveillance but would not be impacted by the introduction of the Hib conjugate vaccine. We defined a case of pneumococcal meningitis as confirmed by blood or CSF culture for a child presenting with clinical meningitis. We analyzed our data using Stata v. 8.2 (College Station, Texas).

Results

Characteristics and Health Care Seeking Pattern of Meningoencephalitis Cases Detected in the Community

In 2008, the field team approached households in 98 of the randomly selected rectangles. Two of the rectangles were in areas under army supervision, and the authorities did not grant permission for house to house interviews. Among 11 380 households in the 98 rectangles, 9632 had children < age 5 years, and the field team secured consent and completed interviews in 9458 (98%). In these 9458 households, parents described 149 episodes of illness among their children <5 years of age that met the suspect meningoencephalitis case definition. Patients who sought care at the surveillance hospital were similar, in terms of severity of disease (seizures >30 minutes; or altered mental status >6 hours; or unconsciousness >1 hour), to patients who did not seek care there (Table I). Among the cases that sought care at the surveillance hospital, 65% were male compared with 45% among the cases who did not seek care at the hospital ($P = .02$). Over their entire illness duration, 48 (32%) cases sought care at either of the 2 catchment area hospitals. Among the cases of suspect meningoencephalitis who did not seek care at the catchment hospital, 57% sought care from other Bachelor of Medicine and Bachelor of Surgery qualified physicians in the vicinity (Table I).

Hospital-Based Surveillance

In the hospital-based surveillance, 958 patients <1 year of age arising from the catchment area of the hospitals were enrolled between May 1, 2008 and September 30, 2011, as possible cases of Hib meningitis. Among the 958 enrollees, 13 cases had laboratory evidence of Hib meningitis with 11 cases detected in the prevaccine period and 2 cases detected in the postvaccine period. Among these 2 cases, 1 had received only 1 dose of the pentavalent vaccine and the other had not received the vaccine at all. Seven (54%) of the cases were between 1-5 months and 6 (46%) were between 6-11 months. Six of the 11 cases (47%) were detected by culture alone with the remaining episodes being diagnosed by Hib

antigen CSF LATs (38%) and urinary latex agglutination (15%). The median CSF white cell count for cases was 600 cells/mm^3. There were no deaths recorded among the patients with laboratory-confirmed Hib meningitis (Table II).

Vaccine Preventable Incidence of Hib and Pyogenic Meningitis after Introduction of Hib Conjugate Vaccine in the National Immunization Program

The incidence of laboratory-confirmed Hib meningitis per 100 000 child-years among infants in the prevaccine period was 91.9 (Table III). The incidence declined to 15.7 cases per 100 000 child-years in infants a year after introduction of the vaccine. From the difference in rates between the pre- and postvaccine periods, the calculated vaccine preventable incidence of laboratory diagnosed Hib meningitis was 76 per 100 000 child-years of observation (95% CI 18-135 per 10^5 child-years) and that of laboratory-confirmed purulent meningitis was 500 per 100 000 child-years (95% CI 203-799 per 10^5 child-years). The preventable proportion of Hib meningitis was 83% and that of purulent meningitis was 30%. The annual incidence of laboratory-confirmed pneumococcal meningitis did not significantly differ between the pre- and postvaccine periods (Table III).

In the prevaccine immunization coverage survey, conducted during 2008-2009, 95% of children had received the third dose of DTP by the age of 12 months. Likewise, 93% of similarly-aged children had received the third dose of the pentavalent vaccine in the postvaccine period survey conducted in 2010-2011.

Discussion

In contrast to the belief that Hib disease is rare in Asia,[13-17] our study demonstrated a high prevaccine incidence of confirmed Hib meningitis (92 per 100 000) in Bangladeshi infants, with an even higher vaccine preventable annual incidence of 500 per 100 000 child-years. Moreover, the Hib conjugate vaccine prevented over 6 times as many cases of purulent meningitis as laboratory-confirmed Hib meningitis. Extrapolating the vaccine preventable incidence rate to the 2.8 million <1-year-olds[18] living in Bangladesh suggests that the vaccine prevented about 14 000 cases attributable to Hib meningitis in the entire country.

Less Hib meningitis in Bangladesh means increased child survival and child health. Children with laboratory-confirmed Hib meningitis have a case fatality of 22%, and another 24% of the cases develop long-term neurologic sequelae.[2] The results of this study suggest that an estimated 3121 infant deaths and 3405 cases of neurologic sequelae resulting from Hib meningitis were prevented annually. However, we do not know if children who were diagnosed as purulent meningitis but attributable to Hib who were not diagnosed as Hib meningitis by the laboratory have the same outcome as cases who have been diagnosed with confirmed Hib meningitis.

These data provide insight on how the burden of Hib can be easily underestimated. Most of the cases of purulent meningitis that were due to Hib were negative by culture, LAT, and PCR, as shown by the large drop in cases of purulent meningitis following Hib conjugate vaccine introduction. Even in this setting of an excellent microbiology laboratory, the vast majority of cases of Hib meningitis prevented by the vaccine were not confirmed as Hib

and, therefore, not attributed to Hib meningitis. The sensitivity of the Hib diagnostic tests are not 100%, especially in the context of high levels of antimicrobial treatment before samples are obtained. In a previous study in the Dhaka Shishu Microbiology laboratory, 53% of CSF samples had evidence of antibiotics.[19] India does not detect much Hib meningitis in diagnostic laboratories,[15] and hence, many health authorities conclude that there is not much Hib meningitis in their country, a conclusion that these data from Bangladesh suggest is likely erroneous.

Our observations demonstrate that even very high-performing laboratories will not detect the vast majority of the cases of Hib meningitis, and, therefore, only considering microbiologically-confirmed Hib cases will drastically underestimate the burden of disease. Moreover, meningitis represents only part of the burden of Hib disease. An estimated 5 cases of pneumonia occur for each case of meningitis.[20,21] Extrapolating the vaccine preventable estimate of 500 cases of Hib meningitis per 100 000 would estimate the incidence of Hib pneumonia in Bangladesh at 4000 cases per 100 000 child-years and extrapolating this rate further to the 2.8 million <1-year-olds[18] living in all Bangladesh suggests that if the vaccine is as effective in preventing pneumonia as it was in preventing meningitis the vaccine prevented about 112 000 cases of Hib pneumonia in the entire country.

The study demonstrated that routine immunization with Hib conjugate vaccines produced a significant reduction in the burden of Hib meningitis even in its first year of introduction. We used the detection of invasive pneumococcal meningitis as a comparison indicator for secular trends in prior treatment, surveillance practices, and laboratory methods that could have offered alternative explanations for this reduction. The incidence of pneumococcal meningitis remained the same but Hib and purulent meningitis dropped notably, which strongly suggests that the reductions in purulent and Hib meningitis were due to the Hib conjugate vaccine introduction. High levels of coverage for DTP 3/pentavalent 3 also enabled us to show impact of disease reduction in the first year of introduction.

Hib conjugate vaccine reduces nasopharyngeal colonization in vaccinated children, which also protects unvaccinated children by reducing exposure to the Hib pathogen. Routine introduction of the Hib conjugate vaccine in the Gambian EPI in 1997 demonstrated that direct impact of the vaccine contributed only 40% of the total population effects that were observed.[22] Herd protection can result from the reduction in the transmission of the target pathogen in a population in which a proportion of the population become immune due to vaccination,[22] and represent important additional benefits of investment in vaccination, especially by low-income countries with limited resources.

A primary limitation of the study is that we have calculated the impact of the vaccination program only among children <12 months old because this was when we had the maximum person-time of vaccinated children and this is the age group in which incidence is highest. This could underestimate the vaccine impact because, as the vaccination program continues, greater herd immunity would be expected to further reduce circulation of the bacteria by reducing nasopharyngeal carriage and further reduce burden even among the unvaccinated <12-month-olds. However, as seen from the age structure of Hib cases detected in earlier

hospital-based studies conducted in Bangladesh,[2] most of the cases of meningitis occurred during the first year of life, and, hence, our analysis provides an early but useful and conservative estimate of the impact of the program.

Second, our adjusted incidence assumes that children who sought care at the surveillance hospital had a similar likelihood of having Hib meningitis as those that sought care elsewhere. Children who received care at the surveillance hospitals and children who did not had similarly severe symptoms. If there was a systematic difference in the proportion of cases of Hib seeking care inside versus outside the surveillance hospital this may affect the adjusted incidence estimates, but we would expect that any such effect would be equivalent in the pre- and postvaccine periods, and therefore, would not bias the impact assessment.

Third, our incidence and impact was calculated in a particular urban area of the country. This may not reflect the national burden of Hib disease as rates of disease may differ in other parts of the country where people live under different living conditions; however, we have no reason to believe that rates would be markedly different elsewhere in the country.

Fourth, not every child received a lumbar puncture. The rate of lumber puncture among cases of suspected meningitis in the surveillance hospitals in the pre- and postvaccine periods were 71% and 73%, respectively (unpublished data from hospital surveillance). Children who did not receive a lumbar puncture could not become a laboratory-confirmed case of purulent meningitis. Therefore, we almost certainly underestimated the burden of purulent meningitis. However, our data demonstrate that the rates of lumbar puncture were similar in the year before and the year after vaccine introduction, and therefore, this would be expected to consistently underestimate burden of Hib disease.

This study provides credible estimates of burden of Hib meningitis and shows initial, conservative effectiveness of the Hib conjugate vaccine in its first year of introduction through the national EPI. The study has important implications for other low-income countries and can act as an important tool to encourage the introduction of Hib conjugate vaccine into routine immunization programs of countries where the burden of Hib disease is high but there is limited capacity to conduct population-based surveillance. The impact of the vaccination program on the reduction of Hib meningitis provides evidence to support continuation of the Hib conjugate vaccine in the EPI schedule of Bangladesh. Further cost effectiveness studies and studies that evaluate impact after several years of implementation could provide further evidence as the stewards of Bangladesh and neighboring countries consider retention of Hib conjugate vaccine in the EPI schedule.

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Glossary

CSF	Cerebrospinal fluid
DTP	Diphtheria-tetanus-pertussis
EPI	Expanded Program on Immunization
Hib	*Haemophilus influenzae* type b
LAT	Latex agglutination test
PCR	Polymerase chain reaction

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Table I

Demographic characteristics and reported clinical signs of suspect meningoencephalitis patients by admission at catchment area hospital, Dhaka, Bangladesh, 2008

Characteristics	Admitted at study hospital (N = 48) # (%)	Not admitted at study hospital (N = 101) # (%)	*P* value
Male	31 (65)	45 (45)	.02
Age-group			
<6 mo	2 (4)	2 (2)	.48
6-12 mo	0 (0)	6 (6)	.08
>12 mo	46 (96)	93 (92)	.36
Reported clinical signs			
Seizures >30 min	22 (46)	40 (40)	.49
Altered mental status >6 h	30 (63)	70 (69)	.47
Unconsciousness >1 h	14 (29)	27 (27)	.79

Table II

Characteristics of laboratory-confirmed Hib meningitis cases (N = 13), Dhaka, Bangladesh, 2011

Characteristics	Number	(%)
Clinical description		
Fever	13	100
Convulsion >30 min	2	14
Reduced level of consciousness	3	23
Bulging fontanelle	6	46
CSF white blood count, median	600	
Age at diagnosis		
0-5 mo	5	38
6-11 mo	8	62
Laboratory results		
CSF culture-confirmed	6	47
CSF latex-confirmed	5	38
Urinary latex-confirmed (1:32) dilution	2	15

Table III

Impact on incidence and effectiveness of introduction of Hib conjugate vaccine in the national EPI program on Hib, as well as pyogenic meningitis

Meningitis	Period	Cases #	<1-year- old children in the catchment area	Total person-time in years at risk for entire catchment area[*,†]	Crude incidence rate per 100 000 child-years	Crude incidence rate difference, 95% CI in cases/10^5 child-years	Adjusted annual incidence rate per 100 000 child-years[‡]	Adjusted incidence rate difference, 95% CI in cases/100 000 child-years
Hib meningitis	Prevaccine	11	38 795	37 423	29	24 (6, 43)	91.9	76 (18, 135)
	Postvaccine	2	35 484	39 890	5.0		15.7	
Purulent meningitis[†]	Prevaccine	197	38 795	37 322	528		1659	501 (203, 799)
	Postvaccine	147	35 484	39 812	369	159 (64, 253)	1159	
S pneumoniae meningitis	Prevaccine	4	38 795	37 422	11	−8.2 (3.4, 17.6)	33.4	−14 (63.5, 36.2)
	Postvaccine	6	35 484	39 887	15		47.0	

[*] Total person-time for infants in 1748 rectangles (total catchment area) is projected from the observed person time for the children in the 98 rectangles.

[†] Total person-time is somewhat less for purulent meningitis than for Hib meningitis as there were more cases of purulent meningitis detected in the laboratories and, hence, these cases contributed less person-time to the denominator than the smaller number of cases detected by the surveillance system as confirmed Hib meningitis.

[‡] Adjusted for the (32%) of children that use the hospital during illness such as meningoencephalitis.